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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/825,911	04/16/2004	Xinli Lin	544112000200	8875

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EXAMINER	
CHOWDHURY, IQBAL HOSSAIN	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 12/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/825,911	LIN, XINLI	
	Examiner	Art Unit	
	Iqbal Chowdhury, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/05& 4/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application is a non-provisional of provisional application of 60/463,632 and 60/498134.

The application filed on 04/16/2004 is acknowledged. Claims 1-24 are pending.

Applicant's election without traverse of Group I claims 1-23 in the communication filed on 11/11/2005 is acknowledged. Claim 23 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1 – 23 are at issue and are present for examination.

Claim Objections

Claim 1 is objected to because of the following informalities: an "and" should be inserted after part (b) and before part (c). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite and vague for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 7 is indefinite and vague in the recitation of "buffer is pH about 10.0". Does it mean "the pH of buffer is about 10.0".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 3-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to method of producing a recombinant pro-urokinase, a precursor of urokinase encoded by a genus of DNA molecule encoding any polypeptide pro-urokinase from any source. The specification teaches the structure of only a single representative species of such recombinant proteins. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of encoding a polypeptide pro-urokinase. Urokinase is a serine protease that cleaves plasminogen to produce active plasmin, also known as plasminogen activator either cellular, tissue or urinary specific based on their distribution in the different compartments of human body. Given this lack of description of representative species encompassed by the genus of DNA used in the methods of the claim to produce recombinant pro-urokinase, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 1, and 3-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of producing refolded recombinant human pro-urokinase, a precursor of urokinase, does not reasonably provide enablement for methods of producing for any pro-urokinase from any source. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 1, and 3-23 are so broad as to encompass methods for the production of any recombinant pro-urokinase. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the large number of recombinant pro-urokinase broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the amino acid sequence of only one human recombinant pro-urokinase.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple point mutations or substitutions.

The specification does not support the broad scope of the claims which encompass methods of refolding any recombinant human pro-urokinase because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting

recombinant pro-urokinase activity; (B) the general tolerance of recombinant pro-urokinase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any recombinant pro-urokinase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including methods of using any recombinant pro-urokinase. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of recombinant pro-urokinase to use in the claimed methods having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 7, 12-13 and 17-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Hua et al. (BBRC, 220: p131-136, 1996, see IDS). Hua et al. (1996) teach the cloning and recombinant expression of human recombinant pro-urokinase gene in E. coli and inducing the

protein expression by IPTG induction and lysing with lysing buffer. The methods of producing refolded and renatured pro-urokinase by Hua et al. (1996) include isolation of recombinant pro-urokinase protein as insoluble inclusion bodies from E. coli, washing the pro-urokinase associated with inclusion bodies with washing buffer and solubilizing the protein by treating with denaturing buffer containing high concentration of chaotroph which comprises 8M urea, 50mM β-mercaptoethanol, sodium phosphate buffer pH from 8-12 and maximum solubilization occurred at pH 10.5-11.0. Hua et al. (1996) also teach the 50 fold dilution of solubilized pro-urokinase in refolding or renaturation buffer comprising 2.5M urea, 1.25mM glutathione, 0.25mM oxidized glutathione and basic amino acid lysine or arginine at 10mM concentration at pH 7.5 for 18-24 hrs.

Claims 1-3, 5-8, 14, and 17-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Hui et al. (Chinese Medical Journal, 114: p186-190, 2001, see IDS). Hui et al. (2001) teach the cloning and recombinant expression of human recombinant pro-urokinase gene in E. coli and inducing the protein expression by IPTG followed by lysing and isolation of inclusion bodies followed by washing before denaturation. The basic denaturation conditions of pro-urokinase are treating the inclusion bodies comprising the pro-urokinase with 5M urea or 6M Guanidine –HCl, 10mM DTT with wide range of pH from 4.0-12.0 with maximum renaturation at pH 8.6-8.8 and the renaturation conditions are dilution of denatured pro-urokinase solution 100 fold in renaturation buffer comprising 2.5M urea, 1mM glutathione at pH 8.6-8.8. In another instance Hui et al. further showed that denatured pro-urokinase was 100 fold diluted in renaturation buffer containing 0.2mM oxidized glutathione, 8M urea and further mixed with 2.5M urea and 0.1mM oxidized glutathione to get better renatured pro-urokinase. Similarly, in another instance Hui et

al. also checked the effect of low concentration Guanidine-HCl at 0.8-1.2M in the renaturation process.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hua et al. or Hui et al. in view of Fahey et al. (2000, see IDS). Hua et al. and Hui et al. are discussed above and each teach methods of refolding human pro-urokinase as claimed in claim 1. However Hua

et al. and Hui et al. do not teach further purification of the refolded human pro-urokinase. Fahey et al. disclose the purification of recombinant pro-urokinase expressed in E. coli as inclusion bodies after denaturation and refolding processes. Fahey et al. purified pro-urokinase by Ion Exchange Chromatography and Size Exclusion Chromatography and used the gel type Sephacryl S-100-400 and maximum active urokinase was achieved by S-300-400 Sephacryl gel.

Therefore, it would have been obvious to one to ordinary skills in the art to purify recombinant pro-urokinase polypeptide expressed in E. coli as inclusion bodies after denaturation and refolding processes as taught by the Hua et al. or Hui et al. through Ion Exchange Chromatography and Size Exclusion Chromatography as disclosed by Fahey et al.

Claims 19-20 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hua et al. or Hui et al. in view of Orsini et al. (Eur. J. Biochem, 195: p691-697, 1991, see IDS). Hua et al. and Hui et al. are discussed above and each teach methods of refolding human pro-urokinase as claimed in claim 1. However Hua et al. and Hui et al. do not teach further purification of the refolded human pro-urokinase. Orsini et al. (2000) teach the purification of recombinant pro-urokinase expressed in E. coli as inclusion bodies. Orsini et al. (2000) purified pro-urokinase by Size Exclusion Chromatography including the gel type Sephacryl S-200 and hydroxyapatite column chromatography.

Therefore, it would have been obvious to one to ordinary skills in the art to purify recombinant pro-urokinase polypeptide expressed in E. coli as inclusion bodies after denaturation and renaturation processes as taught by the Hua et al. or Hui et al. through Size Exclusion Chromatography including the gel type Sephacryl S-200 and hydroxyapatite column chromatography as disclosed by Orsini et al.

Claims 19 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hua et al. or Hui et al. in view of Vairel et al. (US Patent 4106992, see IDS). Hua et al. and Hui et al. are discussed above and each teach methods of refolding human pro-urokinase as claimed in

claim 1. However Hua et al. and Hui et al. do not teach further purification of the refolded human pro-urokinase. Vairel et al. teach the purification of urokinase by DEAE cellulose exclusion chromatography followed by the ammonium sulphate precipitation and finally Heparin Affinity Chromatography.

Therefore, it would have been obvious to one to ordinary skills in the art to purify recombinant pro-urokinase polypeptide expressed in E. coli as inclusion bodies after denaturation and renaturation processes as taught by the Hua et al. or Hui et al. through Heparin Affinity Chromatography as disclosed by Vairel et al.

Claims 9-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hua et al. and Hui et al. Hua et al. and Hui et al. are discussed above and each teach methods of denaturation and refolding of human pro-urokinase as claimed in claim 1 and both teach the concentration of pro-urokinase during the renaturation is important to maximum solubility such that it would be obvious to optimize the concentration of pro-urokinase to one of skill in the art. Hui et al. also mention that having to use very large volumes during renaturation is difficult such that it would make sense to adjust the concentration of pro-urokinase before dilution to limit the amount of volume during renaturation. Hua et al. and Hui et al. both also teach use of beta-mercaptoethanol, DTT, urea, guanidine-HCl, glutathione, oxidized glutathione lysine and arginine and that the concentrations of these are important factors for the solubility of pro-urokinase such that it would have been obvious for a skill artisan to optimize the concentration of each of these components of the renaturation buffer to enhance the solubility of pro-urokinase. Hui et al further teach the 50-fold dilution of denatured human pro-urokinase solution in refolding buffer in the processes of refolding of the recombinant human pro-urokinase and the use of basic amino acid Arginine at 10mM concentration which help refolding process. Hui et al. also disclosed the dilution of denatured pro-urokinase solution to 100 fold in refolding buffer. Therefore, it would have been obvious to one to ordinary skills in the art to dilute denatured pro-

urokinase solution in refolding buffer to optimize the dilution to 20 fold as disclosed by Hua and motivated the use of basic amino acid Arginine at 0.2M concentration in the refolding buffer as disclosed by Hui et al.

Conclusion

Status of the claims:

Claims 1-23 are pending.

Claims 1-23 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury, Ph.D. whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 703-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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